Azithromycin Compared with β-Lactam Antibiotic Treatment Failures in Pneumococcal Infections of Children

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Objective: To determine whether treatment failures occurred more commonly with azithromycin than with β-lactam antibiotics in children who developed invasive pneumococcal disease within 30 days of receiving prior antimicrobial therapy.

Methods: Retrospective review of medical records of children evaluated at Texas Children's Hospital between 1996 and 2002 who had received antimicrobials (azithromycin or a β-lactam antibiotic) and developed invasive pneumococcal disease within 30 days. Treatment failure was defined as invasive pneumococcal infection that occurred while taking antimicrobials or within 3 days of stopping azithromycin treatment or 1 day of stopping β-lactam treatment. Penicillin and azithromycin susceptibilities were determined and categorized according to National Committee for Clinical Laboratory Standards guidelines.

Results: We identified 21 and 33 children with similar demographic features who had developed invasive pneumococcal disease within 1 month of receiving azithromycin or a β-lactam antibiotic, respectively. Eleven (52%) children in the azithromycin group and 11 (33%) in the β-lactam group met the definition for treatment failures ($P = 0.34$). Eight treatment failures while receiving azithromycin were caused by pneumococci with the macrolide-resistant (M) phenotype, 2 with the macrolide-, lincosamide- and streptogramin B-resistant (MLS_B) phenotype and 1 by a macrolide-susceptible organism. In the β-lactam group 7 had a penicillin-resistant isolate, 3 had an intermediately susceptible isolate and 1 had a susceptible isolate.

Conclusions: Our study suggests that treatment failures among patients who developed invasive disease within 30 days of receiving an antimicrobial occur as frequently in patients who receive β-lactam antibiotics as in those who receive azithromycin. Furthermore macrolide resistant organisms are not more likely to be recovered after a macrolide treatment failure than a penicillin-nonsusceptible isolate being recovered after a β-lactam treatment failure ($P = 1.0$).

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In children <24 months of age, *Streptococcus pneumoniae* is the most common cause of meningitis and bacteremia without a source. It is also the major bacterial etiology of acute sinusitis, acute otitis media and pneumonia in the pediatric population. In the year 2000, 58,000 cases of invasive pneumococcal disease occurred in the United States with a death rate of 2.3/100,000.[1]

In the United States, ~35% of pneumococcal clinical isolates are resistant to penicillin and 26% are resistant to erythromycin.[2] Methylation of ribosomal targets, encoded by the *ermB* gene, confers cross-resistance to macrolides (M), lincosamides (L) and streptogramin B (S_B) (the MLS_B phenotype). Isolates that possess this gene usually have high grade resistance, i.e. MIC to erythromycin exceeding 64 μg/ml. *S. pneumoniae* strains possessing the M phenotype have an efflux pump alteration, encoded by *mefE* gene, that causes the active efflux of 14- and 15-membered macrolides from the cell, but they remain susceptible to lincosamides and streptogramin B. This efflux mechanism (M phenotype) accounts for 70% of erythromycin resistance in the United States.[2] The efflux mechanism results in a lower level of resistance (erythromycin MIC between 1 and 32 μg/ml). Nucleotide mutations of the 23S ribosomal RNA and mutations of ribosomal proteins are less common mechanisms of macrolide resistance of *S. pneumoniae*.[3,4]

Although a decrease in the *in vitro* activity of many antimicrobial agents against *S. pneumoniae* has been documented in the last decade,[5] some investigators question the clinical significance of this resistance.[6,7] In the case of macrolides, it has been suggested that the number of macrolide treatment failures is underreported,[8] whereas other authors argue that the paucity of macrolide treatment failures reported is a testament to sustained macrolide efficacy.[6] However, the reports of clinical failures in patients from whom macrolide-

resistant strains (resulting from both the efflux and methylase mechanisms) have been isolated suggest that macrolide resistance is clinically relevant.[4,8–12]

In the case of β-lactam antibiotics, despite an increasing prevalence of pneumococci with reduced susceptibility to penicillin and extended spectrum cephalosporins, treatment failures of β-lactam antibiotics in patients with non-central nervous system pneumococcal infections are infrequently reported.[13–18]

We hypothesized that if treatment failures occurred more commonly with azithromycin than with β-lactam antibiotics, then a greater proportion of children who had received azithromycin would be considered treatment failures than those who received a β-lactam antibiotic among children with invasive pneumococcal disease who had received one of these antibiotics within the month before the invasive infection.

MATERIALS AND METHODS

Since 1993 we have prospectively identified children with invasive infections caused by *S. pneumoniae* in the inpatient and outpatient setting at Texas Children's Hospital, Houston, TX. Pneumococci isolated from these patients are recovered from the microbiology laboratory and sent to the Infectious Disease Research Laboratory where they are coded and frozen at −80°C in horse blood. Clinical and demographic data collected by a research nurse using a standardized form (via chart reviews, telephone interviews to primary physicians and patient's parents) are recorded (Institutional Review Board of Baylor College of Medicine-approved) and maintained in a computer database.

Bacterial Isolates. Penicillin and azithromycin susceptibilities were determined by the microbroth dilution method and categorized according to National Committee for Clinical Laboratory Standards guidelines for azithromycin (susceptible, MIC < 0.5 μg/ml; intermediate, MIC $= 0.5$ to 1 μg/ml; and resistant, MIC ≥ 2 μg/ml) and for penicillin (susceptible, MIC ≤ 0.06 μg/ml; intermediate, 0.12 to 1 μg/ml; and resistant, MIC > 2 μg/ml).

Macrolide-resistant phenotypes were determined by agar disc diffusion with erythromycin and clindamycin discs. Isolates resistant to erythromycin and susceptible to clindamycin were identified as M phenotype, and those resistant to both erythromycin and clindamycin were identified as MLS_B phenotype.

The MLS_B phenotype was confirmed by probing for the *ermB* gene amplified by PCR. DNA samples were prepared from overnight cultures on trypticase soy agar plates with 5% sheep blood (BD Biosciences, Cockeysville, MD). Briefly, bacteria from one agar plate were harvested in 700 μl of saline (0.9% NaCl). After centrifugation at 15,000 × *g* in a microcentrifuge, the pellet was used for DNA extraction using the UltraClean Microbial DNA Kit (Mo Bio Laboratories, Inc., Solana Beach, CA) as recommended. Approximately 200 ng of genomic DNA were used as templates in the subsequent PCRs with primers and conditions previously described.[19]

Study Population. From the pneumococcal surveillance database, we identified patients who had developed invasive pneumococcal disease while receiving azithromycin or after completing a treatment course with azithromycin in the previous month (azithromycin group). We then selected a subset of otherwise normal patients (β-lactam *vs.* azithromycin , 2:1 ratio) who had developed invasive pneumococcal infection while receiving therapy or after completing a treatment course with a β-lactam antibiotic in the previous month (β-lactam group). Patients in this subset were selected based on age and year in which the invasive pneumococcal infection occurred to closely resemble the macrolide group. Medical records were reviewed for both groups based on a standardized form containing the following information: (1) demographic information; (2) date the antibiotic treatment was started and date the antibiotic was discontinued; (3) the diagnosis for which the antibiotic was prescribed; (4) worsening or improvement of that condition while receiving antibiotic therapy.

We defined treatment failures as invasive pneumococcal infection that occurred while taking antimicrobials or within 3 days of stopping the azithromycin or within 1 day of stopping the β-lactam antibiotic treatments. These cutoff values were selected based on the pharmacokinetics of the respective antibiotic. Patients who met the definition of treatment failure but had received antibiotics for <24 h were excluded.

Statistical Analysis. Statistical analysis was performed with SPSS for Windows Version 10.0 software (1999). The Mann-Whitney *U* test was used to compare continuous variables without normal distribution, and the χ^2 test was used for dichotomous variables. All analyses were two tailed. An assessment of the power of the study to detect differences between the groups utilized True Epistat.[20] $P < 0.05$ was considered statistically significant.

RESULTS

Between 1996 and 2002, 29 patients presented to Texas Children's Hospital with invasive pneumococcal infection while receiving azithromycin therapy or within 1 month of completion of treatment. Five children had underlying illnesses (acute lymphocytic leukemia, chronic myelogenous leukemia, recent renal transplant, recent bone marrow transplant, systemic lupus erythematosus on steroid pulses) and were excluded from the study. Three children were excluded because their medical records were not available. None of the patients in the β-lactam group had an underlying medical condition. Twenty-one and 33 patients in the azithromycin and β-lactam groups, respectively, developed an invasive

infection while on therapy or within 1 month of stopping the antibiotic (Figure 1).

Demographic and Clinical Information. No differences in the demographic characteristics between groups were found (Table 1). The most common indication for initiation of antimicrobial therapy in both groups was otitis media. All patients in the azithromycin group received the antibiotic in oral form. In the β-lactam group, four patients were given ceftriaxone intramuscularly for fever without a source. The remainder received an oral β-lactam antibiotic. Azithromycin was given for a median of 4 days (range, 1 to 5 days). A β-lactam antibiotic was given for a median of 5 days (range, 1 to 21 days). Fifty-seven percent of the patients in the azithromycin group were admitted to the hospital with the diagnosis of pneumonia, whereas meningitis was the most common admitting diagnosis in the β-lactam group (33%) (Table 2).

Antibiotic Susceptibilities. All but 3 (18 of 21) isolates in the azithromycin group were resistant to macrolides; 12 (57%) were of the M phenotype and 6 (29%) had the MLS_B phenotype (all 6 contained the *ermB*). Seventeen isolates recovered from patients on azithromycin were available for MIC determinations. Three of the isolates with the MLS_B mechanism of resistance and with an MIC of ≥128 μg/ml for azithromycin were susceptible to penicillin. Three of the 5 patients in the azithromycin group who developed meningitis had a macrolide-susceptible organism.

In the β-lactam group 32 isolates were available for testing. Thirteen isolates (40%) were resistant to penicillin, 7 (21%) were intermediate and 12 (36%) were susceptible to penicillin.

We found that among patients who had developed invasive disease within 30 days of receiving azithromycin or

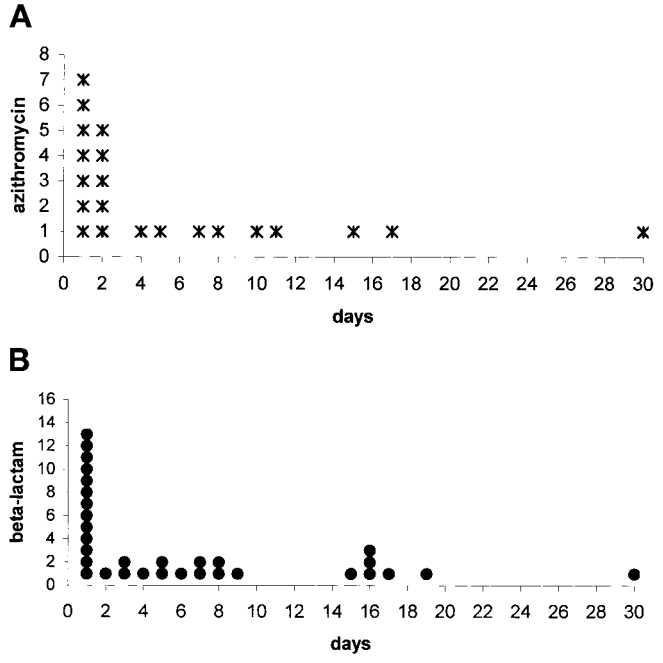

FIGURE 1. *A,* interval between last dose and isolation of *S. pneumoniae* from normally sterile body fluid (abscissa) in patients who received azithromycin within 30 days of development of an invasive pneumococcal infection. *, a single case (ordinate). *B,* interval between last dose and isolation of *S. pneumoniae* from normally sterile body fluid in patients who had received a β-lactam antibiotic within 30 days of development of an invasive pneumococcal infection (abscissa). ●, a single case (ordinate).

TABLE 1. Characteristics of Children Who Received Azithromycin or a β-Lactam Antibiotic Within the Month Before an Invasive Pneumococcal Infection

Characteristics	Azithromycin Group (n = 21)	β-Lactam Group (n = 33)	P
Age (yrs; median, range)	1.51 (0.43–8.9)	1.2 (0.33–15)	0.81
Race			0.31
Caucasian	10 (48)*	11 (33)	
Black	8 (38)	10 (30)	
Hispanic	3 (14)	10 (30)	
Other	0	2 (6)	
Gender			0.37
Male	14 (67)	18 (55)	
Female	7 (33)	15 (45)	
Indication for antibiotic			0.18
Otitis media	14 (67)	14 (42)	
Pneumonia	3 (14)	4 (12)	
Respiratory illness other than pneumonia	3 (14)	3 (9)	
Sinusitis	1 (5)	5 (15)	
Fever without a source	0	4 (12)	
Other	0	3 (9)	

*Numbers in parentheses, percentages unless otherwise indicated.

TABLE 2. Diagnosis at Admission to Texas Children's Hospital of Children Who Received Azithromycin or a β-Lactam Antibiotic Within the Month Before an Invasive Pneumococcal Infection

Admission Diagnosis	Azithromycin (n = 21)	β-Lactam (n = 33)	P
Pneumonia	12 (57)*	9 (27)	0.085
Meningitis	5 (24)	11 (33)	0.39
Mastoiditis	2 (10)	3 (9)	0.64
Bacteremia	2 (10)	8 (24)	0.44
Other	0	2 (6)	0.8

*Number in parentheses, percent.

a β-lactam antibiotic, there was the same chance of developing invasive disease with a macrolide-resistant isolate when taking azithromycin as of developing invasive disease with a penicillin-nonsusceptible (isolates intermediately susceptible or resistant to penicillin) isolate when taking a β-lactam antibiotic ($P = 0.67$).

Treatment Failures. Among the 21 and 33 patients included in the azithromycin and β-lactam groups, 11 (52%) and 11 (33%), respectively, were considered to be treatment failures ($P = 0.24$).

In the azithromycin group (Table 3), the most common indication for the antibiotic was otitis media (9 of 11, 82%), whereas pneumonia was the most common diagnosis of admission. In the β-lactam group (Table 4), 6 (54%) patients were prescribed a β-lactam for the treatment of otitis media. Four patients (36%) were admitted with pneumonia, and 3 (27%) were admitted with meningitis.

Of the patients who failed treatment while receiving azithromycin, eight illnesses (73%) were caused by pneumococci with the M phenotype (MIC ranging from 4 to 32 μg/ml in the six isolates available for testing), two (18%) with the MLS_B phenotype and one (9%) by macrolide-susceptible organisms. The one patient with a susceptible organism developed meningitis. In the β-lactam group of patients who failed treatment, seven (64%) had penicillin-resistant isolates (MIC 2 to 4 μg/ml), three (27%) had an isolate of intermediate susceptibility and one (9%) had a susceptible isolate.

When we compared patients with treatment failure according to the antibiotic received and susceptibility of the strain, we found that macrolide-resistant organisms were no more likely to be recovered after a macrolide treatment failure than for a penicillin-nonsusceptible isolate to be recovered after a β-lactam treatment failure ($P = 1.0$).

DISCUSSION

Because of its once daily dosing schedule, azithromycin has gained popularity among pediatricians for the treatment of upper respiratory tract infections. Hyde et al.[5] recently reported a 32% increase in macrolide use for the pediatric population younger than 5 years of age. β-Lactam antibiotics, however, remain the agents of choice for the treatment of acute otitis media, sinusitis and pneumococcal pneumonia in pediatric patients.[21–23] Perhaps the most appropriate indication for the use of azithromycin is in children 5 years of age or older in whom community-acquired pneumonia is likely to be caused by an organism such as *Chlamydia pneumoniae* or *Mycoplasma pneumoniae*.[24,25] Furthermore the efficacy of azithromycin in the treatment of invasive pneumococcal infections in children has not been well-studied, and the increase of macrolide resistance among pneumococcal isolates raises further concerns about its use in children with invasive pneumococcal disease.

Treatment failures or breakthrough bacteremia have been reported with β-lactam and macrolide antibiotics during the treatment of pneumococcal infections. The significance of *in vitro* resistance with regard to treatment failures related to the use of these agents is becoming clearer. Intermediate penicillin resistance appears to be of little clinical significance in the treatment of pneumococcal pneumonia or sepsis. For non-central nervous system infections, β-lactam antibiotics reach concentrations at the site of infection that are 10-fold higher than the concentration considered necessary for the treatment of pneumococcal isolates which show intermediate susceptibility to penicillin. Therefore standard β-lactam therapy is recommended.[14,26–28] Despite this, treatment failures for invasive pneumococcal infections in pa-

TABLE 3. Pneumococcal Isolates Recovered From Children Who Had Received Azithromycin in the 30 Days Before an Invasive Infection and Developed Treatment Failures

Isolate	Indication*	Admission Diagnosis	Phenotype	MIC (μg/ml)
1	Respiratory illness†	Pneumonia	MLS_B	>128
2	Otitis media	Pneumonia	MLS_B	>128
3	Otitis media	Pneumonia	M	4
4	Otitis media	Bacteremia	M	32
5	Otitis media	Meningitis	M	N/A
6	Pneumonia	Pneumonia	M	4
7	Otitis media	Pneumonia	M	4
8	Otitis media	Pneumonia	M	16
9	Otitis media	Pneumonia	M	16
10	Otitis media	Mastoiditis	M	N/A
11	Otitis media	Meningitis	S	.125

*For antibiotic before admission.
†Respiratory illness other than pneumonia.
S, susceptible; N/A, not available.

TABLE 4. Pneumococcal Isolates Recovered From Children Who Had Received a β-Lactam Antibiotic in the 30 days Before an Invasive Infection and Developed Treatment Failures

Isolate	Indication*	β-Lactam	Duration† (Days)	Admission Diagnosis	Penicillin MIC (μg/ml)	Isolation Site
1	Otitis media	Cefaclor	16	Mastoiditis	4	Retroauricular abscess
2	Otitis media	Cefaclor	9	Mastoiditis	1	Middle ear
3	Otitis media	Cefprozil	5	Bacteremia	1	Blood
4	Otitis media	Amoxicillin	3	Meningitis	2	Blood
5	Otitis media	Amoxicillin	4	Pneumonia	4	Blood
6	Fever	Ceftriaxone	3	Pneumonia	4	Blood
7	Respiratory illness	Amoxicillin	4	Pneumonia	2	Pleural fluid
8	Respiratory illness	Cefprozil	3	Meningitis	0.008	Cerebrospinal fluid
9	Sinusitis	Cefixime	4	Pneumonia	4	Pleural fluid
10	Otitis media	Amoxicillin	7	Arthritis	2	Synovial fluid
11	Fever	Cefuroxime	2	Meningitis	0.5	Blood

*For antibiotic before admission.
†Number of days the antibiotic was taken before admission.

tients receiving β-lactam antibiotics have been reported, especially with cephalosporins.[15–18] In the present study the majority of patients who had treatment failures on a β-lactam antibiotic (64%) had a penicillin-resistant isolate. This is in agreement with recent case reports of treatment failures, where the isolates also were resistant to penicillin.[15–18] Forty-five percent of patients in this study had received either amoxicillin or amoxicillin/clavulanate previously and failed treatment. Because the dose prescribed for these antibiotics is not known, a lower dose could possibly account for the treatment failure, particularly in the setting of resistant isolates.

It has been proposed that because of the pharmacokinetic and pharmacodynamic properties of azithromycin, the low levels of resistance exhibited by some strains (as noted for the M phenotype) may be overcome by the high concentrations of drug achieved in body fluids, cells and tissues despite the low serum levels achieved.[7,29] Several case reports and a case-control study have reported failure of macrolide antibiotic treatment in patients with macrolide-resistant isolates with either M or MLS_B phenotypes (Table 5).[4,8–12] Noreddin et al.,[30] using a pharmacodynamic model to simulate achievable concentrations of clarithromycin in serum and epithelial linings, found that serum concentrations of this drug failed to eradicate *mef*(A) strains with MICs ≥2 μg/ml but that concentrations achieved with the same dose in the epithelial lining fluid were able to eradicate completely those isolates that were macrolide-susceptible as well as those *mef*(A) strains with MICs of ≤8 μg/ml.[30]

In the United States M phenotype isolates have increased in frequency, especially among pneumococci recovered from children <5 years of age, whereas the proportion of pneumococcal isolates with the MLS_B phenotype has remained stable.[12] Moreover there has been an increase in the erythromycin MIC_{50} in the isolates with the M phenotype (from 4 μg/ml to 8 μg/ml).[12] In our study 11 children during a 6-year period failed treatment while receiving azithromycin therapy (Table 3). To our knowledge this represents the largest number of such children reported to date. Of the 7 isolates from our patients who developed pneumonia after treatment failure, 4 had azithromycin MICs of ≥16 μg/ml. Three of our patients who developed pneumonia had isolates with the M phenotype and an azithromycin MIC of 4 μg/ml. Lonks et al.[8] also reported a patient with the diagnosis of pneumonia who experienced macrolide (received azithromycin orally for 3 doses) treatment failure with an M phenotype isolate and an azithromycin MIC of 4 μg/ml. These data suggest that the efflux mechanism of resistance may have clinical significance, even for isolates with azithromycin MIC as low as 4 μg/ml.

Musher et al.[4] recently described a patient who developed pneumococcal infection with an azithromycin-resistant isolate while receiving intravenous azithromycin. The MIC of the initial pneumococcal isolate was 0.008 μg/ml, whereas MICs of subsequent isolates were 2 to 4 μg/ml. Butler et al.[31] also reported a patient who developed an isolate resistant to macrolides while receiving azithromycin. Our patients did not have blood cultures drawn before the initiation of therapy; therefore we were unable to determine whether the organisms were already resistant to azithromycin or whether resistance developed during therapy.

The results of this study suggest that pneumococcal treatment failures among patients who developed invasive pneumococcal disease within 30 days of receiving antimicro-

TABLE 5. Reported Patients Receiving Macrolide Therapy for Pneumococcal Infection with a Treatment Failure

Authors	Age	Macrolide	Indication	Admission Diagnosis	Days Taken	Interval*	MIC (μg/ml)	Phenotype	Mortality
Kelley et al.[9]	46 yr	Azithromycin	LLL infiltrate	Pneumonia	3	0	8[†]	M	Survived
	58 yr	Azithromycin	Bronchitis	Pneumonia	5	3	16[†]	M	Survived
	77 yr	Clarithromycin	Fever and cough	Pneumonia	3	0	8d	M	Survived
	5 yr	Azithromycin	Otitis media	Otitis media, bacteremia	5	1	16[†]	M	Survived
Fogarty et al.[10]	44 yr	Azithromycin	Cough, chills	Pneumonia	4	0	8[‡]	M	Survived
	65 yr	Azithromycin	Cough	Pneumonia	5	0	8[‡]	N/A	Survived
	52 yr	Azithromycin	Cough, pleuritic chest pain	Pneumonia	3	0	>128[‡]	MLS_B	Survived
Reid et al.[11]	8 mo	Clarithromycin	Otitis media	Meningitis	5	0	2[†] 4[‡]	N/A	Survived
Jackson et al.[12]	10 mo	Azithromycin	Otitis media	Meningitis	4	0	>256[†]	N/A	Survived
Kays et al.[3]	53 yr	Azithromycin	CAP	Pneumonia	3	0	>32[‡]	23 S rRNA mutation	Survived
Musher et al.[4]	28 yr	Azithromycin	CAP	Pneumonia	4	0	0.008[‡§] 2–4[¶]	23 S rRNA mutation	Died
Butler et al.[31]	46 yr	Erythromycin	CAP	Endocarditis, epidural abscess	N/A	N/A	≤0.2[‡§] 100[¶]	23 S rRNA mutation	Survived
Lonks et al.[8§‖]	2 yr	Azithromycin	N/A	N/A	2	N/A	>128[‡]	MLS_B	N/A
	1 yr	Azithromycin	N/A	N/A	2	N/A	>128[‡]	MLS_B	N/A
	2 yr	Josamycin	N/A	N/A	4	N/A	>128[‡]	MLS_B	N/A
	1 yr	Clarithromycin	N/A	N/A	4	N/A	>128[‡]	MLS_B	N/A
	1 yr	Azithromycin	N/A	N/A	3	N/A	>128[‡]	MLS_B	N/A
	1 yr	Azithromycin	N/A	N/A	4	N/A	>128[‡]	MLS_B	N/A

*Interval between last dose and bacteremia.
[†]Erythromycin.
[‡]Azithromycin.
[§]MIC (micrograms/ml) of organism before starting therapy.
[¶]MIC (μg/ml) of organism while receiving therapy
[‖]Children in the study by Lonks et al.[8]
LLL, left lower lobe; CAP, community-acquired pneumonia; rRNA, ribosomal RNA; N/A, not available.

bials occurred as frequently in patients taking a β-lactam antibiotic as in those who received azithromycin therapy. Our data suggest that resistance contributed to the treatment failures in both groups. However, other factors not assessed in this study such as dose, bioavailability of the drug, compliance or virulence of the organism also were likely to be important. Limitations of this study include that it had sufficient numbers to detect a difference of only 38% with 80% power or 44% with 90% power with an α of 0.05 in the proportion with treatment failures between the antibiotic groups and that only patients who had taken the drugs and developed invasive disease within 30 days were included. To accurately validate our conclusions, a prospective study of breakthrough invasive infections in children in the community who have been prescribed azithromycin or a β-lactam antibiotic must be performed.

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